



Johnson & Johnson
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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
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Docket No. 2003D-0206

**FDA Draft Guidance for Industry on Exocrine Pancreatic Insufficiency Drug Products;
Submitting New Drug Applications**

Dear Sir/Madam:

Johnson & Johnson appreciates the opportunity to comment on FDA's Draft Guidance for Industry, *Exocrine Pancreatic Insufficiency Drug Products; Submitting New Drug Applications*. It is evident from the guidance that the Agency thoughtfully developed its recommendations regarding information that should be included in applications for pancreatic enzyme products (PEPs). Enclosed please find our comments on the guidance, including elaboration on the following recommendations:

- The Agency should interpret the NDA requirements with respect to PEPs in light of the substantial amount of safety and effectiveness information that is already known about such products.
- The guidance should be revised to reflect an acceptable variation in release percentage; manufacturers may be able to reduce the amount of overage, but due to the nature of PEPs, will not be able to achieve 100% of label-claim potency.
- The Agency should consider accepting alternative test methods to establish efficacy and bioavailability (e.g., breath tests).

Thank you for considering our comments.

Sincerely,

2003D-0206

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Comments on the Draft Guidance for Industry Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs

General Comments

Pancreatic enzyme products (PEPs) have been on the US market for over 65 years. As can be expected, the scientific community and PEP manufacturers have accumulated a substantial body of data and information regarding PEPs. PEPs are the subject of numerous studies in published literature, all of which are available to the Agency. As FDA acknowledges in the draft guidance, there is a considerable body of evidence that replacement of pancreatic enzymes provides clinical benefit to patients with cystic fibrosis (CF) and chronic pancreatitis (lines 216-217). The Agency has even established recommendations on a starting dose titration and maximum dose for PEPs (lines 282-284). We therefore believe the Agency should interpret the NDA requirements with respect to PEPs in light of the substantial amount of safety and effectiveness information that is already known about such products. For example, we believe the Agency should accept *all* NDAs submitted under the guidance (i.e., not just applications submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act) with published articles and bibliographies of clinical trials in lieu of clinical data (lines 239-240). To the extent the Agency decides not to amend the general recommendations provided in the draft guidance, we ask that the specific comments described below be considered.

Specific Comments

II Background

Lines 83-89

This paragraph in the draft guidance explains the rationale behind the Agency's conclusion that manufacturers are unlikely to obtain approval of pancreatic extract products (PEPs) as ANDAs submitted under section 505(j) of the Act. To clarify the relationship between section 505(j) of the Act and ANDAs, we suggest adding the following sentence at the beginning of the paragraph, "An ANDA is described in section 505(j) of the Act as an application that contains information to show that the proposed product is identical in active ingredient, dosage form, strength, route of administration, labeling, quality, performance characteristics, and intended use, among other things, to a previously approved reference listed drug."

III Chemistry, Manufacturing, and Controls Section of the Application

C. Stability

Lines 154 – 156

Primary stability studies should be performed with batches that are formulated to be released at 100 percent of the label-claimed potency. The proposed shelf life should not depend on the existence of a stability overage.

We recommend the guidance be revised to allow for some variability in release percentage. The USP allows for a significant overage (90%-150 or 165%), and as a result manufacturers conduct primary stability studies with batches formulated to be released with an overage. If the guidance document is not revised to allow for an overage, manufacturers will find it difficult to meet the enzyme specifications at expiry on product manufactured to 100% label-claim.

D. Overages

Lines 162 – 165

The finished product should be formulated to be released at 100 percent of the label-claimed potency to reflect accurate labeling, to reduce batch-to-batch variability in potency, and to reduce the amount of accumulated degradants in the product. As a result, patients will at no time receive a much higher or lower dose than intended, a possible safety concern”.

As previously noted, we recommend the guidance be revised to reflect an acceptable variation in release percentage. FDA’s guidance that the finished product should be formulated to release at 100 percent of the label-claimed potency does not reflect the current USP specifications and establishes an unrealistic expectation that manufacturers will be able to produce PEPs without any overages. Manufacturers may be able to reduce the amount of overage, but due to the nature of PEPs, will not be able to achieve 100% of label-claim potency because the product will not be able to meet enzyme specifications through its expiry date if it is released at 100% label-claim. Manufacturers should address potential safety concerns related to product overage in the labeling for the product.

IV. Nonclinical Pharmacology and Toxicology Section

B. Pharmacology

Lines 196-199

FDA recommends applicants to summarize the published literature about the pharmacology of PEPs and submit this summary with a bibliography as part of a 505(b)(2) application. In addition, we encourage submission of all available nonclinical information including any pharmacological data generated with the drug substance and/or drug product.

Given the vast number of potential reference documents to be summarized, FDA's recommendation would require duplication of substantial efforts among manufacturers of PEPs. To obtain summary information regarding PEPs, we suggest FDA rely on summary publications that are already generally available, e.g., the Thompson MICROMEDEX databases and Drugdex Drug Evaluations for Pancrelipase.

V. Human Pharmacokinetics and Bioavailability Section

Lines 204 –207

The bioactivity and/or bioavailability of the active ingredients should be determined at the site of action (gastrointestinal tract). The lipase, amylase, and protease activities should be determined from aspirates from the stomach and duodenum. The data should be obtained under fasting conditions as well as after a standard meal stimulation.

We recommend that more details be provided regarding the studies FDA expects to receive in applications for PEPs. For example:

- **Study subjects:** We believe these studies should be conducted in the target population, i.e., patients suffering from cystic fibrosis (CF). Some literature suggests that release of the drug products (enzymes) from the formulation could be affected by the magnitude of pH differences that are reasonable to expect in CF patients relative to healthy subjects. Because CF affects pediatric patients, bioactivity/bioavailability studies should be conducted in this population.
- **Dose:** The guidance document should specify single dose versus multiple doses and indicate that dose should be normalized to account for differences in formulation strength across products.
- **Conditions:** Lines 206-207 indicate that data should be obtained after a standard meal stimulation. We understand that a standard meal for CF patients includes high fat and high protein, and that due to steatorrhea and generalized

malabsorption, CF patients often require greater than 150% RDA requirements for nutrients. In the final guidance document, we recommend that FDA elaborate on its expectations regarding appropriate standard meals for adult and pediatric patients with steatorrhea and malabsorption.

- Reference Standard: FDA should clarify whether bioactivity or bioavailability should be estimated against a reference standard. Furthermore, clarification should be provided regarding whether statistical analyses should be performed to support equivalent or complete enzyme release.
- Primary bioavailability/bioactivity endpoint: FDA should clarify its expectations regarding the primary bioactivity/bioavailability endpoint, i.e., whether a pharmacodynamic endpoint can be studied as a surrogate for bioactivity. FDA should also provide guidance on how baseline activity should be measured.
- Method: FDA should provide guidance on the type of techniques manufacturers should employ to determine the bioactivity of PEPs. The feasibility of testing the *in vivo* bioactivity of pancreatic enzymes cannot easily be performed without invasive techniques. This has been done in adult CF patients (Butt, A.M., Ip, W., Ellis, L., et al., 2001, "The Fate of Ingested Enzymes in CF," *Pediatric Pulm*, 22 (suppl), 137-138.). In children, the use of gastrostomy tubes for supplemental enteral nutrition would provide access for testing bioactivity and, therefore, would facilitate such a task. However, the ¹³C- Mixed Triglyceride Breath Test could be employed to assess lipase activity. The advantages of this method are as follows: (a) the endpoint (i.e. carbon dioxide production) is obtained by a non-invasive method and correlates with efficacy of pancreatic enzymes; (b) efficacy is related to physiological site of digestion in the duodenum; and (c) the method is simpler than fecal fat collection and easily performed in adults and children. We request that the final guidance document reflect FDA's current thinking regarding the techniques that could be employed.

Lines 209 – 211

The use of any inactive ingredient in the formulation to prevent or minimize the hydrolysis of the enzymes in the stomach should be supported with in vitro and/or in vivo release data. An appropriate in vitro release test method should be developed.

We recommend that FDA provide guidance regarding the appropriate *in vitro* release test methods that should be employed pursuant to the guidance. Pancrelipase-containing products are used by patients suffering from CF. The pathobiology of CF is very different from physiological changes exhibited in other chronic pancreatitis conditions. A characterization of the pathophysiology of the CF intestine has revealed that the microenvironment of the CF GI tract and intestine is different than the *in vitro* testing conditions used for assay of pancreatic enzymes. Factors that may affect the dissolution of enteric coated pancreatic enzyme products include: abnormal gastric emptying in CF; small bowel overgrowth; bile acid malabsorption in CF, shortened transit time for

assimilation of nutrients and other intra-luminal factors including mucus hypersecretion. The study by Butt et al. clearly demonstrates that the dissolution of enteric-coated products does not empty within the CF intestine as presumed from the manufacturing process.

VI. Clinical Studies for New PEPs (Section 505(b))

We recommend that FDA provide specific guidance regarding the use of pharmacodynamic measurements, including the use of non-invasive breath testing analysis, to assess fat malabsorption as a validated measure for clinical trials. The studies using breath testing could address endpoints such as efficacy and identification and confirmation of duodenal dissolution and release of a pancrelipase containing product, since in the absence of improvement in steatorrhea or surrogate measure of steatorrhea, pancreatic enzymes would not be released into the duodenum.